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October 2, 2000
Dr. Stuart L. Nightingale, MD
Senior Medical Advisor to the Assitant Secretary for Planning and Evaluation
Office of the Secretary
Dept of Health and Human Services
200 Independance Ave, SW Room 447D
Washington, DC 20201

Dear Dr. Nightingale,

Enclosed please find the manuscript from Citizens for Responsible Care and Research (CIRCARE) for dissemination of the proceedings from the August 15/16, 2000 Conference on Human Subject Protection and Financial Conflict of Interest at the NIH. Two text copies and an electronic version are included.

Thank you for the opportunity.

I am
Yours Sincerely –
Marie M. Cassidy

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Citizens for Responsible Care & Research (CIRCARE)

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We believe that the public interest cannot be well served at public policy conferences and advisory board meetings if the public interest is not adequately represented. CIRCARE is a self-funded non-profit organization of concerned professionals and lay individuals whose primary objective is to improve the existing safeguards for all human subjects of research: Although not invited to participate in the regular program devised for the August 15/6 Conference on Conflicts of Interest we appreciate the limited opportunity to offer our perspective in the public commentary section. We believe this is reflective of the pattern of exclusion that characterizes a culture of insularity. The Federal Register asked a series of questions pertaining to the currently operative protections in research on human subjects. In the past several years, CIRCARE has assembled a significant database extremely relevant to the questions posed for this multiagency hearing, complete with comprehensive bibliography, which documents ethical, medical, and legal abuses in human research AND reports on any novel, institutional, professional, and federal efforts to ameliorate a system which has provoked considerable public distrust. Based on such knowledge, therefore, as we believe to exist, we will first address some issues generated for this public discourse from our frame of reference.

Commentary on Questions Posed for This Conference

Conflicts of interest in the human experimentation industry are not the exception; they are the defining characteristic of the industry. This is a result of the unimpeded control by a confluence of self-interest groups; foremost among them are the pharmaceutical corporate sponsors, their partners in academia, and public agency officials who are not empowered to shield industry from public oversight and accountability. This collusion has resulted in illegitimate research practices that disregard the rights and welfare of individual human subjects – when such practices serve their financial interests. Financial conflicts of interest are at the root of informed consent violations; the financial interests of sponsors, investigators, and institutions collide with the public interest and governing bodies do not properly represent the public interest.

The current system's failure to protect human subjects from abuse has come to light as a result of information provided to the press. We will address only question #2: Is there empirical evidence of how Conflict of Interest adversely affects the safety of human subjects? We believe the other questions ignore entirely the essence and scope of the problem, which is that multimillion-dollar clinical studies, are critical to medical center budgets and provide incentives to push ahead with projects despite potential risks for individual human subjects. Furthermore, the collision of money and medicine has come

to influence everyday medical care in ways that few patients may suspect, rewarding doctors with bonuses for every patient they persuade to enroll in a study. Therefore, we believe that these questions demonstrate a cognitive dissonance concerning the current system.

- For example, corporate investor interests supersede considerations of health hazards in the FDA drug approval process: Pfizer's schizophrenia drug, Zeldox (ziprasidone) had been rejected 2 years ago by an FDA advisory panel because of its causal link to fatal ventricular arrhythmia when tested in several thousand human subjects. Zeldox had been shown to prolong the patient's cardiac interval or QT, a condition that can lead to cardiac fibrillation, and in turn, a serious cardiac arrhythmia. Yet, a new panel recommended to approve Zeldox based on a study with only 184 subjects, of whom 163 completed the study. Not that it has been reported that the FDA's so-called "expert" advisory panels are stacked with industry affiliated "experts" it is more likely that financial interests – not the public interest – influenced the panel's decision. The health hazard of the drug remains. Therefore, the panel's recommendation appears to have been influenced by the fact that the FDA's approval of Zeldox will have significant revenue implications: "Pfizer estimates that the drug, launched into a marketplace growing at a 20% annual rate, could potentially net the company up to $1 billion per year."
- Unscrupulous researchers who have ready access to patient rosters are free to recruit them as human subjects for personal cash bonuses. The absence of mandatory restrictions and enforcement policies has resulted in widespread abuse at major medical research centers, which depend on pharmaceutical industry grants. The Federal government is also financing doctors and medical centers that engage in unethical patient recruitment methods that violate patient privacy and our inalienable right to informed consent. For example, a Federal government grant subsidized roughshod recruitment methods by researchers from the University of Illinois at Chicago – elderly people were lured, some harassed, into Alzheimer's studies. According to the findings of the Office of Protection from Research Risks (OPRR), reported in The Chicago Tribune, the elderly were being "stalked, harassed and coerced in participation" by door-to-door recruiters from Chicago's Rush Presbyterian equipped with deceptive, written "talking points".
- Although the drug Propulsid was linked to deaths in adults, the FDA approved a clinical trial exposing 100 children to this potentially fatal drug. As a result, nineteen children died ---including a 9-month old infant. According to the Pittsburgh-Post-Gazette, the parents only learned about the risks associated with Propulsid from an Associated Press report AFTER their baby was dead. The consent form given to the parents falsely indicated that the FDA had approved Propulsid. Reflux, the condition for which Propulsid was prescribed, is not considered a life-threatening condition in and of itself, and doctors say that most babies outgrow the problem by their first birthday. The parents said the doctor conducting the

clinical trial was adamant that Propulsid was the best treatment for their child. If they had known of the previous deaths, the parents said, they never would have consented.

It is significant that litigation forced Janssen Pharmaceutica to stop marketing this drug in the U.S., not Federal proscription. The death of this baby demonstrates how the FDA colluded in a climate of exploitation: The FDA approved consent form signed by parents had misled them by claiming the FDA had approved the drug for pediatric use. We question the wisdom of a policy that encourages the use of children in drug trials BEFORE the safety and efficacy of the drugs has even been established in adults.

- Site based "Academic detailing" is a new scheme for circumventing Federal informed consent requirements. By claiming that a protocol whose purpose is to increase utilization of the drug clozapine (Clozaril) is an "educational" protocol designed to educate psychiatrists, industry paid "academic detailers" obtained a waiver for informed consent from the NYS Mental Hygiene Research Foundation (which oversees all state psychiatric research) and the IRB of Pilgrim Psychiatric Center. They argued and convinced the IRB that the study, "Evaluation of the Use of an Academic Outreach Program to Increase Clozapine utilization in Patients..." did not involve risks for the psychiatrists conducting the research. The patients, who alone would incur serious risks – including two potentially fatal side effects associated with Clozaril – agranulocytosis and neuroleptic malignant syndrome – were simply excluded from consideration. A patient at Pilgrim, who was a non-consenting subject in this protocol, died of neuroleptic malignant syndrome.
- Healthy children – who have not been diagnosed with an illness, but whose siblings have schizophrenia – are being put at high risk of developing disabling, drug-induced symptoms without medical justification nor even solid scientific evidence. A pilot protocol is being conducted at Yale University, exposing 31 youngsters aged 12 to 25 to a powerful antipsychotic drug, olanzapine (Zyprexa) that, in a significant number of patients, has produced serious, potentially irreversible side-effects. The rationale given by researchers who are under contract with Eli Lilly, the sponsoring drug company, is that they hypothesize that these children may be "at risk" for schizophrenia. Since there are, as yet, no objective tests or biological markers for the illness – they hypothesize without solid evidence, merely on the basis of conjecture. The shaky basis for their conjecture is the assumption that the children may develop schizophrenia because one of their siblings has the disorder.

The risk of schizophrenia for the general population is 1%. For siblings the risk increases from 2% to 15% - in other words **there is a 90% likelihood that these children will not develop schizophrenia.** Even for those who already exhibit early signs ("prodromal symptoms"), the estimated risk for developing schizophrenia is highly variable (25-50%) given the absence of scientifically accurate tools for interpreting

psychiatric symptoms. Psychiatrists cannot as yet accurately diagnose schizophrenia, much less predict who will get it. In this experiment, healthy children – who are not capable of giving voluntary, informed consent – are being put at high risk of harm for experimental purposes. "No one knows the long-term dangers of putting such patients on antipsychotic drugs," acknowledged Dr. Rex Cowdry (formerly with NIMH). Doctors in clinical practice and research must have solid medical evidence to justify prescribing medications, particularly powerful psychotic drugs that cause sever, disabling side effect. The Physician Desk Reference (PDR) states that it is unknown how Zyprexa or any other neuroleptic works, and includes a warning about possible serious adverse side effects, sexual dysfunction, seizures, induced mania, potentially-fatal neuroleptic malignant syndrome (NMS), tardive dyskinesia, and acute weight gain (50lbs is not unusual) which significantly increase the risk for diabetes. Additionally, mounting clinical evidence and findings, from non-industry sponsored research point to additional, severe, adverse neurological changes in response to long-term exposure to neuroleptics. Drug action suppresses certain brain receptors (e.g., dopamine, glutamate), and when such drugs are withdrawn (or a patient stops taking them) the drug-induced receptor changes are unmasked, causing an acute "discontinuation syndrome" _i.e., "rebound psychosis") that is often more severe than the original symptoms of the illness.

In pre-marketing clinical trials lasting on average, 6-weeks, olanzapine (Zyprexia) caused serious adverse drug side effects in 22% of patients – only 26% responded favorably. The severe side effects included: Cardiopathology – 10% to 15%; Serious weight gain – 50% had gained 7% of their body weight; Parkinson-like motor dysfunction – 11.7%; Akathesia – 7.3%; **There were 27 deaths during clinical trials of Zyprexia, of which 15 were suicides.** In addition to documented serious adverse drug reactions after short-term exposure to clinical trials, a growing body of evidence, some obtained by photo imaging techniques, demonstrates abnormal, permanent brain receptor alterations and changes in volume of several regions of the brain after exposure to psychotropic drugs.

Although no health system in the world currently identifies adolescents in the pre-onset phase as ill, a consortium of pharmaceutical companies and universities are laying the groundwork to expand Yale's controversial experiment. Without medical or scientific justification – hence in violation of acceptable, ethical standards – 1,500 adolescents are being targeted for a multinational schizophrenia "prevention" experiment. Industry is providing $25 million investment aimed at vastly expanding the already lucrative $5 billion antipsychotic drug market. The Wall Street Journal has aptly noted that "the proposed study raises the question of whether the drug companies are mainly interested in "creating" a new illness that requires drug treatment."

My name is Marie M. Cassidy and I am a professor of Physiology and Experimental Medicine at the George Washington University School of Medicine and Health Sciences in Washington DC. For 4 decades I have been a medical educator and a medical research scientist and am representing the views of Citizens for Responsible Care and Research in this particular forum. This conference would appear to have been designed with the intent of delineating the variety and scope of the conflicts of interests in human research and to generate advice concerning how the present federal guidelines could be implemented and strengthened.

It is clear from the profile of problems recounted at this meeting and which have been the subject of intense media interest in recent years that public trust in research in American medicine may be in jeopardy when the aptly named 'collision of money and medicine' is made explicit. It is ironic that these developments are taking place at a time when the imperative trend in educating and training physicians is oriented towards the graduation of health-care providers fully cognizant of evidence- based medical therapies and experienced in psychosocial and diversity aspects of their professional responsibilities. Yet embedded in the existing guidelines governing research activity with human subjects, eg. 45C46, the Common Rule, is the concept that education, self-reporting and self-regulation by research practitioners and research institutions constitute a shield that adequately protects human subjects. However, this does not reflect normative practice in the real world. These restraint perimeters were originally promulgated in a period of time characterized in part by a wide spectrum of individual, independent, kinder, gentler, physician investigators whose activities spanned both medical care and the search for more refined remedial treatments. In the post-Bayh-Dole era, which facilitated the rapid transfer of technology and the proliferation of the expertise essential to its successful fiscal execution, this point of view may be obsolete and of little practical relevance. The current regulating system is also characterized by several features which are extremely troubling in many respects. The Institutional Review Board System which was established, in part, to assure protection of human subjects in biomedical research are now in the position of functioning as facilitators for the accrual of grant monies by their parent institutions. In practical terms, it is also attuned to post-hoc investigational exercises directed toward abuses which come to light and in which the outcome of positive findings is usually temporary discontinuance of the project and with a new emphasis to be placed on the intrinsic value of funding sanctions. Additionally, as has occurred in the arena of improper conduct in laboratory research, an interlocking and commingling interface with the legal system and the operating parameters thereof is transpiring. Innovative solutions aligned with prophylactic, preventative measures should be of prime consideration, in conjunction with serious sanctions and appropriate punitive measures.

With respect to conflicts of interest there are many permutations both simple and complex. They range from inherent personal ambivalence within an individual healer/researcher to prestige recompense, primary loyalties incumbent on members of an Institutional Review Board to direct financial emoluments and investment/equity portfolios of research teams and institutions. It is patently obvious in this era of the emerging academic/industrial interwoven complex that existent firewalls interposed between traditional academic, scholarly pursuits and commercial exploration of new medical therapies and devices have been extensively breached. Because of serious economic pressures converging on academic medical centers and arising from managed care reductions in reimbursement from all previous sources they are endeavoring to survive financially by becoming co-capitalist entities. Individual physicians in unit or group practices are also increasingly cajoled into providing a patient database substrate to help offset their own declining incomes.

From an objective, dispassionate point of view the myriad minor and severe disregard exhibited for the welfare of human subjects it is possible to assert that the

system now in place is dysfunctional with respect to its proclaimed objectives. The surveillance mechanisms and monitoring specifications were proven inadequate vis a vis the pervasive nature of the problem once the underlying cultural and interconnected practices were revealed.

CIRCARE believes that **SHORT TERM SOLUTIONS** can be inaugurated immediately to address some of the more urgent situations and to terminate immediate further harm. These include

- A moratorium on symptom provocation experiments in schizophrenia research which exacerbate a severe, incapacitating, life-threatening illness.
- A prohibition on conducting non-therapeutic experiments which are above minimal risk on vulnerable persons. Mental capacity for informed consent should be assessed by an independent physician unconnected to the research project .
- Require education and certification of all researchers in ethics and ethical human research procedures.
- Establish a national databank for all human subject enrolled in research, including that comprehensive filing of informed consent documents and provision of an emergency hotline for the reporting of all adverse incidents The Office of Human Research Protection should post the results of its findings into allegations on the OHRP Website in a timely fashion. Prompted by the fact that
  a) Private individuals or institutions conducting research on humans which do not receive Federal Funding nor seek the approval of the FDA for a drug or device NEED NOT abide by the Common Rule and that
  b) Since 1966 the Animal Welfare Act has regulated the use of animals in research, irrespective of the source of funding.

CIRCARE therefore proposes a **LONG TERM SOLUTION** to the current morass. In the accelerating race from research funding to commercially profitable product the need for human research legislative protection has become glaringly apparent. At the conference on The Business of Human Experiments: Ethical Legal and Regulatory Issues, Baltimore, Md. 3-5 Nov. 2000 (Sponsored by Friends Research Inc.) the essential components and features of such a Bill, together with those already introduced will be discussed.